N-terminal B-type natriuretic peptide levels in pediatric patients with congestive heart failure undergoing cardiac surgery

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Objectives: The objectives of this study were to measure circulating N-terminal B-type natriuretic peptide levels in pediatric patients undergoing surgical repair of congenital heart lesions with left ventricular volume overload and to determine whether presurgical and immediate postoperative N-terminal B-type natriuretic peptide levels could predict patient outcomes after surgical intervention.

Methods: Thirty-eight children aged 1 to 36 months undergoing surgical repair of cardiac lesions with left ventricular volume overload were studied. Plasma N-terminal B-type natriuretic peptide levels were measured preoperatively and at 2, 12, 24, 48, and 72 hours after surgical intervention and were assessed for their predictive value of postoperative outcomes. Plasma N-terminal B-type natriuretic peptide levels were also measured in 34 similarly aged healthy children.

Results: Patient preoperative N-terminal B-type natriuretic peptide levels were significantly higher than those of healthy control subjects (3085 $\pm$ 4046 vs 105 $\pm$ 78 pg/mL). Preoperative N-terminal B-type natriuretic peptide levels correlated with the complexity of surgical repair, as measured by cardiopulmonary bypass time ($r = 0.529$, $P < .001$), and with postoperative measures, including fractional inhaled oxygen requirements registered at 12 hours ($r = 0.443$, $P = .005$) and duration of mechanical ventilation ($r = 0.445$, $P = .005$). Plasma N-terminal B-type natriuretic peptide levels increased 5-fold within 12 hours after cardiopulmonary bypass (14,685 $\pm$ 14,317 pg/mL). Multivariable regression analysis showed that the preoperative N-terminal B-type natriuretic peptide level was a significant predictor of duration of intensive care unit stay ($P = .02$) and that the peak postoperative N-terminal B-type natriuretic peptide level was a significant predictor of the intensity of overall medical management, as assessed by using the therapeutic intervention scoring system ($P = .01$).

Conclusion: Plasma N-terminal B-type natriuretic peptide levels measured preoperatively and postoperatively can be a prognostic indicator in the management of the pediatric patient after surgical intervention for congenital heart repair.

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The natriuretic peptides, of which atrial natriuretic peptides and brain or B-type natriuretic peptide (BNP) are of myocardial cell origin, play a significant role in the control of volume homeostasis and regulation of blood pressure.[1-3] Plasma levels of the cardiac natriuretic peptides have been shown to increase with congestive heart failure in adults and to correlate with the severity of disease, thus providing an indirect measure of left ventricular (LV) function.[4-6] The biologically inactive prohormone of BNP (proBNP), is secreted by cardiac ventricular myocytes in response to volume and pressure overload[7] and is enzymatically cleaved to the physiologically active form, BNP, and the inactive N-terminal fragment, NT-pro-BNP or N-BNP, in a one-to-one ratio.[8-10] Circulating levels of

Abbreviations and Acronyms

BNP = B-type natriuretic peptide
CCAVC = complete common atrioventricular canal
CPB = cardiopulmonary bypass
LV = left ventricle
N-BNP = N-terminal B-type natriuretic peptide
PICU = pediatric intensive care unit
TISS = Therapeutic Intervention Scoring System
VSD = ventricular septal defect

both BNP and N-BNP have been shown to be increased in early cardiac dysfunction in adults, making it a useful predictor of congestive heart failure in hypertrophic or dilated cardiomyopathy[4,5,11-14] and a prognostic indicator of outcome in congestive heart failure.[15-18] The recent commercial development of a diagnostic N-BNP assay was based on the greater in vitro stability of this moiety compared with that of BNP and with the longer half-life of circulating N-BNP, making it a reliable marker of cardiac function.[19,20]

Recently, measurements of either BNP or N-BNP as perioperative markers of ventricular function or as prognostic indicators of postoperative outcomes in pediatric patients with congenital heart disease have been explored.[21-24] However, only limited data exist regarding the effects of LV volume overload on the circulating levels of N-BNP in pediatric patients with congenital heart disease. Therefore, the primary goal of this study was to measure circulating levels of N-BNP in pediatric patients with LV volume overload who were undergoing cardiac surgery with cardiopulmonary bypass (CBP) and to correlate preoperative and postoperative N-BNP levels with outcome measures to assess the utility of N-BNP as a reliable marker of postoperative clinical status of the pediatric cardiac patient.

Materials and Methods

Study Inclusion Criteria and Diagnostic Classifications

This prospective study was conducted at Schneider Children's Hospital and was approved by the institutional review board of the North Shore Long Island Jewish Health System. Written informed consent was obtained from parents or guardians before recruitment into the study. Sixty-seven pediatric patients with congenital heart defects known to cause LV volume overload scheduled for complete surgical repair were identified between September 2004 and November 2005 as eligible for enrollment into this study. Thirty-eight of these patients who are included in the present analysis were 3 years of age and younger and had lesions including ventricular septal defect (VSD) and complete common atrioventricular canal (CCAVC). Patients with single-ventricle physiology and obstructive lesions, such as aortic stenosis or coarctation of the aorta, were excluded from the study. Evidence of preoperative renal insufficiency, as indicated by measures of blood urea nitrogen and creatinine, precluded participation.

Control subjects were recruited from healthy patients evaluated during well-care visits to the pediatric clinic at Schneider Children's Hospital. Written informed consent was obtained before enrollment in this study. A history of acute or chronic illness, any prior cardiac disease, or both precluded participation. All subjects had normal physical evaluations and no clinical evidence of congenital heart disease. Blood samples were drawn after the clinical evaluation for subsequent analysis of N-BNP levels.

Data Collection

Clinical data were prospectively collected on intraoperative parameters and postoperative outcomes. Surgical procedures, including CPB and anesthesia, followed standard practices, and postoperative patient management in the pediatric intensive care unit (PICU) were based on standard institutional protocol without knowledge of patient N-BNP test values. Presurgical blood samples were obtained from enrolled patients during outpatient presurgical routine blood analysis. After surgical intervention, patients were admitted to the PICU, with the majority of patients receiving mechanical ventilator support. Blood samples were drawn from central intravenous catheters at 2, 12, 24, 48, and 72 hours after termination of CPB or until the catheters were removed. Therefore, N-BNP analysis at later time points was not obtained on all patients because of the removal of central intravenous lines. Blood samples were processed immediately, and the plasma was stored at −20°C until all samples could be analyzed. Plasma N-BNP levels were measured with a commercially available electrochemiluminescence immunoassay kit (Elecsys proBNP, Roche Diagnostics, NJ).

Patients were continuously monitored in the PICU, and clinical data, including quantities of vasodilator and inotropic drugs, blood gas and lactate analyses, oxygen requirement, urine output, blood pressures, cardiac rhythm, and heart rate, were recorded daily. These values were among 76 different therapeutic and monitoring procedures used to assess the overall degree of postoperative care, as calculated by using the Therapeutic Intervention Scoring System (TISS).[25] TISS scores were derived over a 24-hour period and reflected the invasiveness, intensity, and complexity of care rendered to the patient in the PICU. Inotropic scores were obtained at 24, 48, and 72 hours after CPB by using a modification of the calculation described by Wernovsky and colleagues[26]: Dopamine + Dobutamine + ([Epinephrine + Norepinephrine]) × 100. The daily inotropic score was calculated by obtaining the total amount of inotropic drug administered in a 24-hour period and expressed as micrograms per kilogram per minute.

Statistical Analysis

Plasma N-BNP values were compared between the healthy control group and the presurgical values of the study patients by using *t* tests. A repeated-measures analysis of variance was carried out to compare N-BNP values collected over time (preoperatively and postoperatively at 2, 12, 24, 48, and 72 hours) for the surgical patients. Tukey-adjusted pairwise comparisons were carried out to determine which time points significantly differed from one another. Because age was considered as a potential confounder, all analyses made an adjustment for age by using age as a covariate. It was determined that a log transformation of the data conformed to the standard ANOVA assumptions. Accordingly, all analyses